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(54) **Spherical grains of polyamino acid and production method thereof.**

(57) The present invention provides novel spherical grains of polyamino acid which can be used as a filler in chromatography, cosmetic powder and the like. The spherical grains can be produced by a method which comprises the steps of preparing a solution of hydrophobic polyamino acids, such as poly n-leucine, dissolved in an organic solvent; adding the solution to an aqueous medium and agitating said medium so as to obtain a dispersion of the spherical grains of the polyamino acid dispersed in the aqueous medium while evaporating the organic solvent; and isolating the spherical grains of the polyamino acid from the dispersion.

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Title: Spherical grains of polyamino acid and production method thereof

The present invention relates to spherical grains used for various applications such as a filler in chromatography, a cosmetic powder and also to a method of producing such spherical grains.

Spherical grains of various materials conventionally find various uses such as fillers in various types of chromatography, cosmetic powders, and latices for investigation of biological reactions. Such spherical grains, however, still suffer problems and shortcomings which have to be solved. For example, a spherical particle gel of a dextran-based material, called Sephadex® and frequently used as a filler for gel chromatography, has a drawback in that the strength thereof needs to be increased by conducting a complicated crosslinking procedure because this filler exhibits a low strength under pressure. On the other hand, the amount of the polymers which can be fractionated by using the known filler material is reduced undesirably (in molecular weight terms) as their degree of crosslinking is increased.

The present inventors have found that various properties of spherical grains can be easily controlled by employing polyamino acids, particularly synthetic polyamino acids which is an entirely different raw material as compared to that conventionally used for the applications described above.

Recently, investigations with respect to synthetic polyamino acids have progressed greatly and various applications of synthetic polyamino acids are now expected to be feasible. Moreover, there has been no example of a polyamino acid itself being spherically granulated. The inventors have established a method of producing spherical grains comprising synthetic polyamino acid as a matrix and this has led to the completion of this invention.

It is, therefore, a primary object of the present invention to provide novel spherical grains of polyamino acid which can be used for various applications.

Another object of the present invention is to provide a method for preparing such spherical grains.

These and other objects of the present invention will be clear from the following description.

In accordance with the present invention, there are provided novel spherical grains comprising polyamino acid.

There is also provided a method of producing spherical grains which comprises the steps of adding a solution of a hydrophobic polyamino acid dissolved in an organic solvent to an aqueous medium and agitating the medium while evaporating

the organic solvent so as to obtain a dispersion of the spherical grains of polyamino acid dispersed in the aqueous medium; and isolating the thus obtained spherical grains of polyamino acid from the dispersion.

Fig. 1 is an electron microphotograph showing the surface structure of spherical grains obtained in Example 2 of the present invention;

Fig. 2 is an enlarged electron microphotograph showing a part of the surface structure of the spherical grains shown in Fig. 1;

Fig. 3 is an electron microphotograph showing the surface structure of the spherical grains obtained in Example 4 of the present invention; and

Fig. 4 is an infrared absorption spectrum of the spherical grains obtained in Example 4 of the present invention.

As described above, there has been no conventional technique of spherically granulating a polyamino acid itself. Hitherto, polyamino acids have been fixed to a suitable carrier (for example, polystyrene beads) to provide a suitable material for a separation operation of isomers. The present invention makes use of the fact that spherical grains of hydrophobic polyamino acid can be directly formed by adding a solution of a

particular polyamino acid, that is a hydrophobic polyamino acid dissolved in an organic solvent, to an aqueous medium (in which the solution is insoluble or only slightly soluble) in order to suspend the polyamino acid therein. In the method of the present invention, liquid drops comprising the organic solvent containing a hydrophobic polyamino acid are dispersed in the aqueous medium by adding the above-described solution to the aqueous medium and agitating it. As the agitation proceeds, the organic solvent is gradually evaporated so that a dispersion of the spherical grains of the hydrophobic polyamino acid is obtained in the aqueous medium. Then, the spherical grains of the hydrophobic polyamino acid isolated from the dispersion by suitable separation techniques (for example filtration or centrifugation).

Any kind of polyamino acids can be used in the present invention. The suitable polyamino acids can be easily prepared by a conventional method. A method of preparation of poly(γ-methyl glutamate) is illustrated below by way of example:

(i) preparation of N-carboxy anhydride (hereinafter referred to as NCA)

γ-methyl glutamate is suspended in tetrahydrofuran, after which $COCl_2$ is charged into the solution at a temperature of 40°C to obtain a transparent solution. After the excess $COCl_2$ has been distilled off, the solution is concentrated under reduced pressure, whereby NCA is obtained.

(ii) polymerization of NCA

The thus obtained NCA is dissolved in dichloroethane, and thereafter the NCA is polymerized by adding to the solution 2 to 0.5 equivalents of triethylamine (a polymerization catalyst) relative to NCA. As a result, poly (γ-methyl glutamate) is obtained. In this connection, NCA can easily be prepared by the Leuchs method, the Curtus method or preferably the above-described Fuchs-Fartling method.

In the present invention, polyamino acids having any polymerization degree can be used. However, it is preferable to use a polyamino acid having a polymerization degree of 100 to 5000, more preferably 300 to 3000.

The hydrophobic polyamino acids used for obtaining a dispersion in an aqueous medium in accordance with the present invention includes naturally hydrophobic polyamino acids such as polyalanine, polyvaline, polyleucine, poly n-leucine, polythreonine, polymethionine, polycystine, poly (phenylalanine), polytryptophane, poly(phenylglycine) and the like. Among these polyamino acids, it is preferable to use polyalanine, polyvaline, polyleucine, polymethionine, polycystine, poly(phenylalanine), polytryptophane or poly(phenylglycine). Specific examples for useful polyamino acids are those obtained by converting hydrophilic polyamino acids to hydrophobic polyamino acids (hydrophilic amino acid polymers having hydrophobic groups introduced). Examples for such modified polyamino acids include hydrophobically esterified acid polyamino acids such as polyglutamic acid and aspartic acid, e.g. by alkyl esters such as methyl, ethyl, propyl, t-butyl or octyl

esters: aralkyl esters such as the benzyl ester; cyclohexanemethyl esters; and tetrahydropyranmethyl esters of these amino acids. It is preferred to use the methyl ester, ethyl ester, t-butyl ester, benzyl ester, or the cyclohexane methylester of polyglutamic acid or polyaspartic acid. There can also be used hydrophobically carboxylated basic polyamino acids such as polylysine, polyarginine, polyhistidine, polyornithine, e.g. carbobenzoxylated, carbo-ethoxylated and carbo-t-butoxylated amino acids. It is preferred to use a carbobenzoxylated or carboethoxylated polylysine.

Furthermore, there can be used a polyamino acid prepared by introducing a hydrophobic moiety such as the benzyl group, t-butyl group or acetyl group to a water-soluble neutral polyamino acid such as polyserine. In this case, it is preferable to use O-benzyl polyserine or O-tert-butyl polyserine. When these modified polyamino acids are used, spherical grains of the modified polyamino acids thus obtained may be used without any processing or may be changed into spherical grains of hydrophilic polyamino acids by removing the hydrophobic groups from the hydrophobic polyamino acids, depending on the intended applications. That is to say, spherical grains of hydrophobic and hydrophilic polyamino acids (including amphiphatic polyamino acids) can be finally obtained in accordance with the present invention by employing hydrophobic polyamino acids during the preparation of the dispersion described above.

As described above, the method of the invention employs a solution of a hydrophobic polyamino acid dissolved in an organic solvent. This organic solvent can form liquid drops containing the hydrophobic polyamino acid when the solution is added to the aqueous medium and / is being evaporated by continuously agitating the aqueous medium. Therefore, the organic solvent used in the method of the invention should easily dissolve hydrophobic polyamino acids, be insoluble in water, and have a lower boiling point than that of the aqueous medium. Preferred examples of this organic solvent are chloroform, dichloromethane, dichloroethane, and similar halogenated hydrocarbons, benzene, or a mixture of these solvents.

For the purpose of preparing spherical grains of hydrophobic polyamino acids in accordance with the present invention, a solution of hydrophobic polyamino acids dissolved in an organic solvent is added to an aqueous medium. Such a solution can be obtained by adding hydrophobic polyamino acids in an organic solvent as described above, or, more generally, it can be obtained as a polymerization solution of the hydrophobic polyamino acid and can be used without any processing. In a preferred embodiment of the present invention a solution obtained by polymerizing amino acids in an organic solvent is used and a hydrophobic polyamino acid is obtained without requiring any processing.

The grain size of the spherical grains the polyamino acid obtained can be easily controlled in accordance with the

method of the present invention. The factors which control the grain size are mainly viscosity and the agitation speed of the organic solvent-aqueous medium system employed. In general, the grain diameter of the spherical grains obtained is increased as the polyamino acid concentration in the organic solvent is increased and the viscosity of the aqueous medium system decreases. On the other hand, higher agitation speed causes the spherical grains size to be decreased. When regulating the grain diameter of the spherical grains by controlling the viscosity and the agitation speed of the organic solvent-aqueous medium system, it is preferred to add a viscosity modifier or to regulate the concentration of the polyamino acid solution. Suitable examples of the viscosity modifier are water-soluble polymers such as partially acetylated polyvinyl alcohol and gelatine. When fine grains for use as latices for biological reactions are to be obtained, it is preferable to add emulsifiers such as cetylpyridium salts and sorbic esters.

Furthermore, the invention makes it possible to produce porous spherical grains of opened cell structure, various porosity and pore sizes which can be employed as a filler in gel chromatography or a moisture- or air-permeable cosmetic powder. In order to obtain such porous spherical grains, an additive which is non-compatible with the polyamino acid, compatible with the organic solvent in which the polyamino acid is dissolved, insoluble in the aqueous medium, and which has a higher boiling point than the organic

solvent and the aqueous medium, is added to the solution of the hydrophobic polyamino acid dissolved in the organic solvent. While agitating the solution in the presence of such an additive, liquid drops comprising the organic solvent are formed and the phase of this additive is separated in the polyamino acid solution. Thus, porous spherical grains of hydrophobic polyamino acid can be obtained by removing the additive in the latter processes and the degree of porosity and the pore diameter of the spherical grains can be controlled by adjusting the amount of the additive. The amount of the additive is generally variable in a range of about 1 - 3 parts by weight based on the solid contents contained in the polymer solution, being dependent upon the type of additive selected. As the additives used for obtaining porous spherical grains, a crystalline substance such as naphthalene in a solid form may be added, and generally one may add liquids such as decalin, tetralin, toluene, xylene, ethylbenzene, diethylbenzene, anisole, hexanol, octanol, and dibutyl ether; aliphatic acids, such as oleic acid, linolic acid and the like; and dialkyl phthalate such as dibutyl phthalate, dioctyl phthalate and the like.

According to the invention, it is thus possible to obtain spherical grains comprising polyamino acid as a matrix. Microscopic observation of the polyamino acid spherical grains of the present invention showed that the grains were spheres (particularly in the case of those having a large grain diameter) and that the crystals of polypeptide were formed in

aggregation. The polyamino acid spherical grains of the present invention are characterized by being rigid, as compared with conventionally used spherical grains such as Sephadex®. The infrared absorption spectrum of the spherical grains of the present invention showed that a β-structure is at least partially present, the presence of such a β-structure being considered to further contribute to the hardening. The grain size of the spherical grains of the present invention can be controlled in the required range by producing them in accordance with the above-described method. Generally, the grain size of the spherical grains of the present invention is within the range of 0.1 to 500μ, preferably 1 to 300μ.

Furthermore, the pore diameter and the degree of porosity of the spherical grains of the present invention can be controlled as required over a wide range by producing them making use of the additives for rendering the grains porous, as described above. The pore diameter and the porosity can vary in accordance with the desired application, and the spherical grains obtained by the above-described method of the present invention can be controlled in such a way that one may obtain products having a pore diameter corresponding to a range of 10^2 (maltose) to 10^6 (dextran), in terms of the molecular weight of water-soluble polysaccharide, and a porosity of 10 to 95%. Thus, the spherical grains of the present invention can be controlled such that they maintain a suitable rigidity and possess a desired porosity without the requirement to carry out any hardening treatment such as crosslinking which is necessary with conventional spherical grains.

In accordance with the present invention, spherical grains of hydrophobic polyamino acids can be obtained by using naturally hydrophobic polyamino acids and/or by using modified polyamino acids the raw material of which has been made hydrophobic as described above. Such spherical grains of hydrophobic polyamino acids are particularly suitable for reversed phase chromatography and affinity chromatography. Spherical grains of a modified polyamino acid which is made hydrophobic but which has a relatively low hydrophobic property, that is amphiphatic polyamino acids (for example, polymethyl or polyethyl glutamate), are preferably used as gel grains for utilization in gel chromatography both in water-systems and organic solvent-systems. In addition, the spherical grains of hydrophilic polyamino acids can be formed by removing the hydrophobic groups from the spherical grains obtained by using a modified polyamino acid the raw material of which has been made hydrophobic by conventionally known method. The spherical grains of hydrophilic polyamino acids can be used, for example, as ion-exchange spherical grains. The spherical grains of polyamino acids of the present invention can be used also as a cosmetic powder. Particularly, the porous spherical grains of amphiphatic polyamino acids described above are suitable for such applications.

The advantage of the present invention will be fully understood from the following examples.

Example 1:

5 g of polyleucine dissolved in 250 g of chloroform was dropped in 1000 ml of an aqueous solution containing 2 wt% of partially acetylated polyvinylalcohol and kept at 45°C under agitation so as to suspend the polyleucine therein. After the solution was agitated for 24 hours, chloroform was evaporated, and polyleucine was aggregated to obtain poreless spherical grains. The spherical grains were collected by filtration and adequately washed with hot water and methanol to obtain polyleucine grains having a diameter of 44 to 75 µm at a yield of 80%.

Example 2:

5 g of poly-γ-benzyl-L-glutamate were dissolved in 200 ml of dichloromethane and suspended in an aqueous solution of 15 wt% partially acetylated polyvinylalcohol. After being agitated for 8 hours at 30°C, the suspension obtained was subjected to an after-treatment in accordance with the method used in Example 1 to obtain the intended poreless spherical grains having a diameter of 75 to 200 µm.

Optical microscopic observation of the spherical grains obtained showed that the spherical grains of the present invention were substantially spheres and the polypeptide crystals were formed by aggregation, as shown in Figs. 1 and 2.

Example 3:

3 g of partially dodecylated poly-γ-methylglutamate (a dodecylation rate of 35%) prepared by a conventional method were dissolved in 200 ml of a mixed solvent of dichloroethane/dichloromethane (1/4) and suspended in an aqueous solution containing 3.5 wt% of partially acetylated polyvinylalcohol. The suspension was agitated for 8 hours at 30°C in order to evaporate the mixed solvent to obtain an aqueous dispersion of spherical grains of a partially dodecylated poly-γ-methylglutamate. The dispersion was concentrated by a centrifugal operation so as to separate the spherical grains which were then sieved to obtain poreless spherical grains of partially dodecylated poly-γ-methylglutamate having an average diameter of 5 to 15 μm (the porosity is 10% or less).

Example 4:

10 g of polymethyl glutamate and 10 ml of decalin (an additive for making grains porous) were dissolved in 400 ml of dichloroethane and the resulting solution was dropped in 2000 ml of an aqueous solution of 2 wt% partially acetylated polyvinylalcohol kept at 50°C. After the solution was vigorously agitated for 12 hours at the same temperature as above, dichloroethane was evaporated to obtain the spherical grains of polymethyl glutamate containing decalin. These grains were washed by a Soxhlet extraction method using acetone for removing decalin, then suspended in water, and fractionated into grain size groups by sieves meeting the JIS specification.

The grain diameter of the main product was 25 to 44 μm, 90% or more of the grains obtained having a diameter of 10 to 105 μm. Optical microscopic observation of the grains obtained showed that they were spheres and had the porous structure as shown in Fig. 3. The infrared spectrum of the spherical grains, as shown in Fig. 4, showed peaks of carbonyl groups based on the reversed parallel β-structure (shown by 1 in the figure), the α-helix structure (shown by 2 in the figure), and the parallel β-structure (shown by 3 in the figure). A conventional gel chromatography operation was carried out in an aqueous system for the purpose of estimating the porosity and the pore diameter of the spherical grains obtained. Namely, the spherical grains were charged in a column having an internal diameter of 5 mm and a length of 30 cm and homologues of dextran and maltose, polyhydric alcohols, and heavy water were eluted as standard samples, the relationship between the retention volumes and the molecular weights of the samples being extrapolated to a column void volume, and the molecular weight at this void volume was defined as an exclusion limit molecular weight (which could be considered as the maximum pore diameter). The porosity was calculated from the eluting position of heavy water. As a result, it was found that the spherical grains of poly (γ-methyl glutamate) had a maximum pore diameter corresponding to 8100 in terms of the molecular weight of dextran and a porosity of 70%.

Example 5:

As an additive for making grains porous, 10 g of diethylbenzene or 30 g of n-octanol were dissolved in 400 ml of dichloroethane together with 10 g of polymethyl glutamate, and the spherical grains having the following characteristics were prepared by the same method as in Example 4.

Spherical grain A (using diethylbenzene as the additive for making the grains porous)

Grain diameter of main product: 25 to 44 μm

Maximum pore diameter: 7000 in terms of the molecular weight of dextran

Porosity: 65%

Spherical grain B (using n-octanol as the additive for making the grains porous)

Grain diameter of main product: 25 to 75 μm

Maximum pore diameter: 10000 in terms of the molecular weight of dextran

Porosity: 65%

The spherical grains obtained were packed in a column having an internal diameter of 5 mm and a length of 30 cm and the separation of homologues and isomers of a lower alcohol was investigated using water as an eluate. The results obtained are shown as eluted volume ratios (k' values) in Table 1. As seen from the table, the spherical grains of

polyamino acids of the present invention have excellent separation capability when used as gel grains for reversed phase chromatography. When acceptability for high speed as a filler for gel chromatography was investigated using the above-described column, the pressure loss was only 20 to 23 kg/cm^2 at a high flow rate of 5 ml/min. As a comparison, flow rate examination was carried out using Sephadex® having the same maximum pore diameter as above (G-50). This comparison showed that the maximum flow rate was as small as approximately 2 ml/minute.

Table 1

Sample species	Spherical grain A retention volume k' (ml)		Spherical grain B retention volume k' (ml)	
Ethanol	4.74	0.65	3.69	0.67
iso-Propanol	5.95	1.07	4.41	0.99
iso-Butanol	9.37	2.26	6.58	1.97
tert-Butanol	5.86	1.04	4.48	1.02
sec-Butanol	7.23	1.51	5.01	1.25
n-Butanol	9.37	2.26	6.58	1.97

* The k' values were based on the retention volume of Blue Dextran.

Example 6:

10 g of polyleucine and 20 g of diethylbenzene (an additive for making grains porous) were dissolved in 500 ml of chloroform, and the resulting solution was dropped into an

aqueous solution of 2 wt% partially acetylated polyvinylalcohol kept at 45°C in order to suspend the polyleucine therein. The suspension obtained was continuously agitated for 24 hours to evaporate chloroform and to obtain a dispersion of spherical grains. Soxhlet extraction with methanol was carried out for 6 hours in order to remove diethylbenzene remaining in the grains. The spherical grains were collected by filtration and then washed with methanol and ether to obtain porous spherical grains of polyleucine having a diameter of 44 to 75 m (the maximum pore diameter: 10^5 in terms of the molecular weight of dextran, porosity: 70%) at a yield of 75%.

Example 7:

10 g of polymethyl glutamate and various additives for making grains porous shown in Table 2 were dissolved in 250 ml of dichloroethane and spherical grains were prepared by the same method as in Example 4. The results of the measurements of the maximum pore diameters and the porosities of the grains are shown in Table 2. As can be seen from the table, the spherical grains of the present invention can be prepared so as to have the desired pore diameter and the porosity over a wide range and thus can be prepared so as to fractionate compounds having various molecular weights used as gel for gel chromatography.

Table 2

Additive for making grains porous	Ratio to polyamino acid (wt%)	Exclusion molecular weight for dextran	Porosity (%)
Nothing	0	60	10% or less
Butyl acetate	100	100	19
Toluene	100	150	14
o-Xylene	100	150	17
m-Xylene	200	150	32
p-Xylene	100	150	20
n-Hexanol	100	1,000	16
n-Octanol	100	1,000	37
n-Octanol	300	10,000	65
Diethylbenzene	100	7,000	65
Decalin	100	8,100	70
Decalin	200	50,000	75
methyl dodecanate	200	2,000,000	90

Example 8:

10 g of an alkylester of polyglutamic acid containing dodecyl groups and methyl groups in a ratio of 32:68 as the ester components were dissolved in a mixed solution of 10 ml of decalin and 400 ml of chloroform and the resulting solution was dropped in 2000 ml of an aqueous solution of 25 wt% partially acetylated polyvinylalcohol kept at 50°C. Chloroform was evaporated by vigorously agitating the suspension obtained at the temperature above for 24 hours. The spherical grains obtained were washed with

ether in order to remove decalin, and then filtrated to obtain porous spherical grains. The grain diameter of the main product was 10 μm to 25 μm, 90% or more of the product having a grain diameter of 1 to 44 μm.

The grains had the porosity of 68%.

In order to investigate the properties of the resulting grains as a cosmetic powder, their oil absorption, water absorption, speed of oil absorption and speed of water absorption was measured and compared to those values of conventional cosmetic powders.

1 to 5 g of each sample was precisely weighed on a glass plate, and one droplet of oleic acid was dropped on the center of the sample through a buret at intervals of 3 to 7 seconds, together with sufficient kneading of the whole sample with a spatula. The above procedure was repeated until the end point, i.e., until the sample as a whole became such a hard, putty-like mass that it formed into a spiral when worked with the spatula. Oil absorption was calculated from the following equation, using the oil amount added thereto up to the end point. However, in the case where the putty-like sample could not be formed into a spiral, the end point was determined as the time just before the sample suddenly softened and adhered to the glass plate upon addition of one droplet of oleic acid to the sample. The water absorption was measured by the same procedure as set forth above, except that distilled water was used instead of oleic acid.

$$A = W/S$$

wherein A represents oil absorption or water absorption [ml/g]; W represents the amount of oil or distilled water added up to the end point [ml]; and S represents the weight of the sample [g].

The speed of oil absorption was measured by pressing a predetermined amount of the sample into a cell and then dropping a predetermined amount of oleic acid on the surface of the pressed sample to observe the speed at which the oil was absorbed in the pressed sample. The speed of water absorption was measured with the same method as set forth above, except that distilled water was used.

The results obtained are shown in Table 3.

Table 3

Sample		Oil absorption	Water absorption	Speed of oil absorption	Speed of water absorption
Conventional powder	Fire silica Powder	350	320	o	◎
	Kaolin	50	60	x	◎
	Magnesium aluminium silicate	300	310	o	◎
	Magnesium carbonate	230	210	o	◎
Spherical grain of the present invention		180	90	◎	△

◎ vary rapid　　o rapid

△ relatively rapid　　x very slow

As is obvious from Table 3, spherical grains of the present invention exhibit a suitably high amount of oil absorption and water absorption, a high speed of oil absorption and slow speed of water absorption, compared with conventional powders. As a result, the spherical powder of the present invention has more suitable properties for use as a cosmetic powder.

what is claimed is:

1. Spherical grains comprising a polyamino acid.

2. Spherical grains according to claim 1, wherein the polyamino acid is hydrophobic.

3. Spherical grains according to claim 1, wherein the polyamino acid is hydrophilic.

4. Spherical grains according to claim 1 and 2, wherein the diameter of the grains is between 0.1μ and 500μ.

5. Spherical grains according to any of claims 1 to 4, wherein the polyamino acid contains a ß-structure.

6. Spherical grains according to any of claims 1 to 5, wherein the grains have a porous structure having a pore diameter of 10^2 to 10^6 in terms of the molecular weight of water-soluble polysaccharide, and a porosity of 10 to 95%.

7. A filler for use in chromatography which comprises spherical grains according to any of claims 1 to 6.

8. Cosmetic powder, which comprises spherical grains according to any of claims 1 to 6.

9. A method of producing spherical grains, which comprises the steps of preparing a solution of a hydrophobic polyamino acid dissolved in an organic solvent; adding the solution to an aqueous medium and agitating the medium so as to obtain a dispersion of the spherical grains of the polyamino acid dispersed in the aqueous medium while evaporating the organic solvent; and obtaining the spherical grains of the polyamino acid from the dispersion.

10. A method according to claim 9, characterized by adding to the solution an additive which is non-compatible with the polyamino acid, compatible with the organic solvent in which the polyamino acid is dissolved, and insoluble in the aqueous medium, and which has a higher boiling point than those of the organic solvent and the aqueous medium.

11. A method according to claims 9 and 10, characterized by adding a viscosity modifier to the solution when the spherical grains of the polyamino acid are obtained.

12. A method according to claim 11, characterized in that the viscosity modifier comprises a water-soluble polymer.

13. A method according to any of claims 9 to 12 for producing the spherical grains of any of claims 1 to 6.

14. Use of the spherical grains of any of claims 1 to 6 as a filler material for use in chromatography.

15. Use of the spherical grains of any of claims 1 to 6 in a cosmetic powder.

FIG. 1

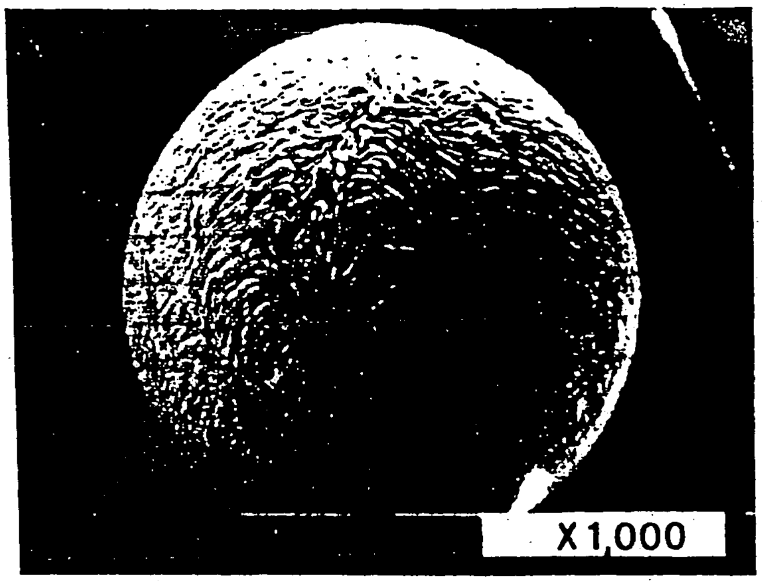


FIG. 2

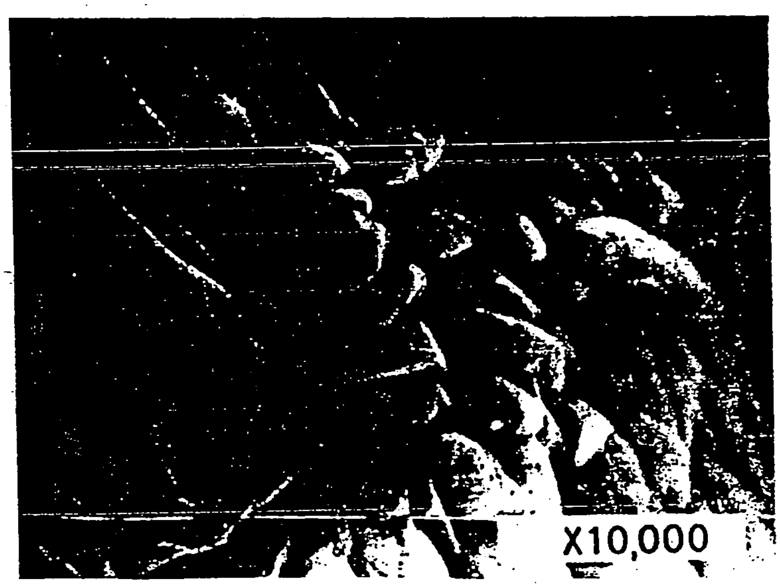


FIG. 3

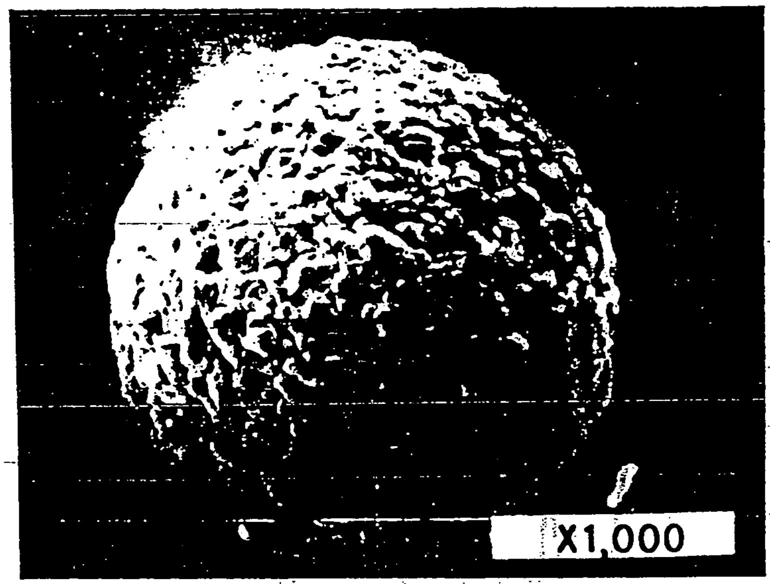
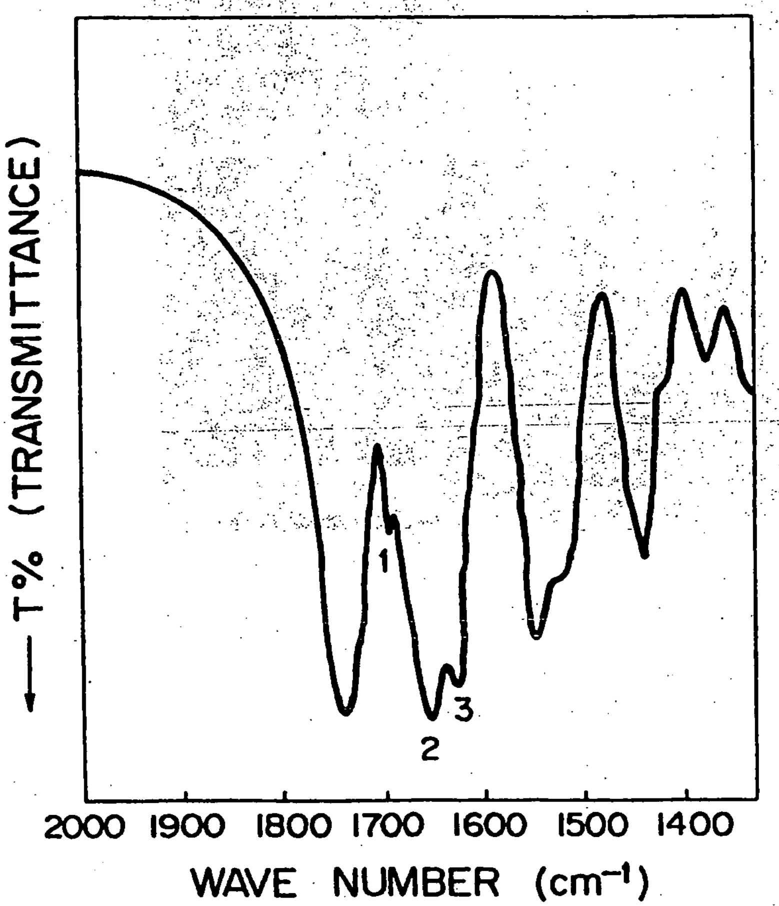


FIG. 4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